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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/073,365	02/13/2002	Yeckezkel Barenholz	BARENHOLTZ=1A	5480

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EXAMINER	
KISHORE, GOLLAMUDI S	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 11/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/073,365	BARENHOLZ ET AL.	
	Examiner	Art Unit	
	Gollamudi S Kishore, Ph.D	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 9-7-04.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 50-55,58-85,88 and 89 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 50-55,58-85,88 and 89 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment after final dated 7-19-04 and the RCE dated 9-1-04 are acknowledged.

Claims included in the prosecution are 50-55, 58-85 and 88-89.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 83, 84 and 85 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The preparation of claim 50 is not in a dry powder form; however, claim 83 which is dependent from 50 refers to the composition as a dry powder.

The distinction between freeze-drying in claim 84 and lyophilization in claim 85 is unclear. Since both are the same, claim 85 is not further limiting claim 84.

Claim Rejections - 35 USC ' 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 61, 63-78 and 80-82 are rejected under 35 U.S.C. 102(b) as being anticipated by Stahl (FEBS Letters, 427, 1998).

Stahl discloses liposomal formulations containing carotenoid, lycopene (note the abstract, Materials and Methods and Tables). The intended use has no significance in composition claims.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that although lycopene is mentioned, there is no teaching in Stahl of encapsulating the antioxidant such as lycopene. This argument is not found to be persuasive since it is very clear from 2.3 on page 305, 'preparation of liposome' of Stahl that the liposomes containing the carotenoids are prepared. Applicant's arguments that lycopene in Stahl is not an active agent as in instant claims are not found to be persuasive since intended use has no significance in composition claims and instant claims do not recite any specific amount of lycopene.

Claim Rejections - 35 USC ' 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 50-55 and 58-62, 65-78, 80, 82-85 and 88-89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stahl cited above.

As pointed out above, Stahl discloses liposomal formulations containing carotenoid, lycopene (note the abstract, Materials and Methods and Tables). According to Stahl, the antioxidant activity of lycopene is greater than other anti-oxidants, alpha-tocopherol, alpha-carotene, beta-cryptoxanthin, Zeaxanthin, beta-carotene and lutein (abstract).

According to the method as disclosed in section 2.3 on page 305, carotenoids, alpha tocopherol or mixtures are dissolved together with phosphatidylcholine in chloroform, the solvent is evaporated and the multilamellar vesicles are prepared by the addition of phosphate buffer followed by sonication. This implies that the carotenoid is added chloroform, which has already dissolved phospholipid. It is unclear from Stahl as to how much phospholipid was used; however, in the absence of showing the criticality, it is deemed obvious to one of ordinary skill in the art to manipulate the amounts of the phospholipid since the phospholipid amounts determine how many liposomes are formed and how much of the lipophilic carotenoids are incorporated in the lipid bilayers. Stahl does not teach cyclohexane as the organic solvent. However, the purpose the solvent is to dissolve the phospholipid, it is deemed obvious to one of ordinary skill in the art to select a suitable solvent as long as it serves the desired purpose. The criticality of phosphatidylcholine obtained from different sources or cyclohexane is not

readily apparent to the examiner in the absence of comparative studies. Stahl does not teach a kit. However, it is deemed obvious to one of ordinary skill in the art to supply the components in the form of a kit so that the artisan can obtain fresh preparations of liposomes when needed. Stahl does not teach that the compositions in a pharmaceutically or cosmetically suited form and that the composition is for the prevention of the damage caused by free radicals. However, since Stahl's studies show that lycopene has greater anti-oxidant activity than other carotenoids, it is deemed obvious to one of ordinary skill in the art to prepare the compositions in a suitable form for the administration and prevention of damage caused by the free radicals.

9. Claims 50-55, 58-85 and 88-89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meybeck in view of Stahl cited above.

The teachings of Meybeck have been discussed before. In essence, Meybeck discloses topical liposomal formulations containing a carotenoid (beta-carotene) for dermatological and cosmetic applications. The applications include, 'fighting aging' and 'protection against sun' (protection against free-radicals, singlet oxygen). The compositions can also be administered orally (abstract, col. 3, lines 19-46; Examples 1 and 17, and claims). The method of preparation of liposomes disclosed by Meybeck is similar to instant method. The method involves dissolving the phospholipid and the carotenoid in an organic solvent and removing the solvent to prepare a dry preparation (as opposed to instant steps where the lipid is first dissolved in the organic solvent and then carotenoid is added to this solution), hydrating the powder with an aqueous

medium and lyophilizing the liposomes and hydrating them again when needed. Although there is no explicit teaching in Meybeck that the liposome forming lipids in the organic solvent is to a level close to saturation, as pointed out above, the amounts of the phospholipid used by Meybeck as seen from examples are more than the amounts noted in instant specification. Assuming that they are different, it is deemed obvious to one of ordinary skill in the art to manipulate the amounts of the phospholipid since the phospholipid amounts determine how many liposomes are formed and how much of the lipophilic carotenoids are incorporated in the lipid bilayers. Meybeck does not teach cyclohexane as the organic solvent. However, the purpose the solvent is to dissolve the phospholipid, it is deemed obvious to one of ordinary skill in the art to select a suitable solvent as long as it serves the desired purpose. Meybeck does not teach a kit. However, it is deemed obvious to one of ordinary skill in the art to supply the components in the form of a kit so that the artisan can obtain fresh preparations of liposomes when needed.

What is also lacking in Meybeck is the teaching that the carotenoid be lycopene. What is also lacking in Smith is the method wherein the phospholipid is dissolved in the solvent first followed by the carotenoid.

As pointed out above, Stahl discloses liposomal formulations containing carotenoid, lycopene (note the abstract, Materials and Methods and Tables). According to Stahl, the antioxidant activity of lycopene is greater than other anti-oxidants, alpha-tocopherol, alpha-carotene, beta-cryptoxanthin, Zeaxanthin, beta-carotene and lutein (abstract). According to the method as disclosed in section 2.3 on page 305,

carotenoids, alpha tocopherol or mixtures are dissolved together with phosphatidylcholine in chloroform, the solvent is evaporated and the multilamellar vesicles are prepared by the addition of phosphate buffer followed by sonication. This implies that the carotenoid is added chloroform, which has already dissolved phospholipid.

It is unclear from Smith as to how much phospholipid was used; however, in the absence of showing the criticality, it is deemed obvious to one of ordinary skill in the art to manipulate the amounts of the phospholipid since the phospholipid amounts determine how many liposomes are formed and how much of the lipophilic carotenoids are incorporated in the lipid bilayers. Stahl does not teach cyclohexane as the organic solvent. However, the purpose the solvent is to dissolve the phospholipid, it is deemed obvious to one of ordinary skill in the art to select a suitable solvent as long as it serves the desired purpose. Stahl does not teach a kit. However, it is deemed obvious to one of ordinary skill in the art to supply the components in the form of a kit so that the artisan can obtain fresh preparations of liposomes when needed.

It would have been obvious to one of ordinary skill in the art to use lycopene as the as the carotenoid in Meybeck's liposomal formulations since Stahl teaches that the antioxidant activity of lycopene is greater than other anti-oxidants, alpha-tocopherol, alpha-carotene, beta-cryptoxanthin, Zeaxanthin, beta-carotene and lutein.

Although this is a new rejection, the examiner would address applicant's arguments regarding the difference in the process of production in Meybeck and in instant application. According to applicant, Meybeck dissolves phospholipid and the

carotenoid in an organic solvent to prepare a dry preparation whereas the instant application first dissolves the lipid in the organic solvent and the carotenoid is added. The statement by Meybeck on col. 3, lines 63-65 is "2g of soya lecithin, and 0.1 g of tretinoin are dissolved in 30 ml dichloromethane in the presence of a lipophilic antioxidizing agent, e.g. 0.0006 g alpha-tocopherol". It would appear from this statement that either lecithin is added to dichloromethane first followed by tretinoin since lecithin is mentioned first. Or the statement could also be interpreted as a mixture of lecithin and tretinoin added together to dichloromethane. Considering the latter as the possibility a proper comparison to show unexpected results would be to compare instant addition of phospholipid first to the solvent to adding a mixture of phospholipid and carotenoid to the solvent.

10. Claims 50-55, 58-85 and 88-89 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 94/13265 (Smith) of record in view of Stahl cited above.

WO discloses liposomal formulations containing beta-carotene for prevention of oxidation damage caused by singlet oxygen and other reactive oxygen species. The liposomes are made from phospholipids including egg phosphatidylcholine. The mode of administration is either topical or oral (capsules or tablets) (abstract, pages 4-6, 9-11, Examples and claims). The method of preparation involves for example dissolving 20 mg of the phospholipid in 2 ml of solvent system together with amphiphilic antioxidants, evaporating to dryness and hydrating the lipid mixture. This implies that the phospholipid is added first to the solvent. What is lacking in WO is the teaching of the carotenoid, lycopene.

As pointed out above, Stahl discloses liposomal formulations containing carotenoid, lycopene (note the abstract, Materials and Methods and Tables). According to Stahl, the antioxidant activity of lycopene is greater than other anti-oxidants, alpha-tocopherol, alpha-carotene, beta-cryptoxanthin, Zeaxanthin, beta-carotene and lutein (abstract).

It would have been obvious to one of ordinary skill in the art to use lycopene as the as the carotenoid in Meybeck's liposomal formulations since Stahl teaches that the antioxidant activity of lycopene is greater than other anti-oxidants, alpha-tocopherol, alpha-carotene, beta-cryptoxanthin, Zeaxanthin, beta-carotene and lutein.

11. Claim 55 is rejected under 35 U.S.C. 103(a) as being unpatentable over Meybeck, or Stahl cited above, further in view of Mackaness (4,192,859).

The teachings of Meybeck and Stahl have been discussed above. What is lacking in Meybeck or Stahl is the use of cyclohexane as the solvent in the preparation of liposomes.

The use of cyclohexane would have been obvious to one of ordinary skill in the art, with the expectation of obtain at least similar results, since Mackaness teaches that organic solvents such as cyclohexane and chloroform could be used in dissolving the phospholipids in the preparation of liposomes (col. 3, lines 40-45).

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that even though Mackaness discloses hexane (cyclohexane) as the solvent to dissolve phospholipids, combining Mackaness with

Meybeck et al would still not lead to the present invention since Meybeck et al dissolve their retinoids in water to form liposomes. The examiner once again points out that applicant is incorrect in stating so since Meybeck does not dissolve the retinoid in water, but dissolves both lecithin and the retinoid in dichloromethane which is an organic solvent.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gollamudi S Kishore, Ph.D
Primary Examiner
Art Unit 1615

GSK